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Dear Aaron:

In responding to your letter of December 4, 1974, I would like to restrict my comments to the question of whether the moratorium should be continued for Type II experiments, as defined in the initial Berg committee letter in Science.

Let me start by making what I believe is an important distinction, a distinction which was a bit fuzzy in the Berg letter and which has continued that way in much of the subsequent discussion. I would like to differentiate clearly between viral or plasmid-viral chimeric nucleic acid molecules which have been made and are being studied in vitro and those same molecules once they have been introduced into a bacterium and have established themselves as replicons in a viable organism. The former are obviously of much less potential hazard than the latter. The efficiency with which DNA or RNA molecules in vitro can establish themselves in cells is very low. Their chemical half-life, to say nothing of their biological half-life, is generally quite short unless they are maintained in sterile solutions of appropriate composition. There should thus be no prohibition against making, by biochemical means, virtually any chimeric DNA or RNA molecule. Standard precautions for working with low risk agents, as defined by the NCI, will suffice for safe handling of these molecules in vitro.

The more difficult question, of course, is what to do about chimeric molecules in which viral genes have been incorporated into plasmid or phage DNA's, and the chimeric DNA's have been established in E. coli. Here again it is useful to make distinctions. I see little risk in establishing, for instance, fragments of SV40 DNA containing one or several of the late genes in E. coli. In fact, as we discussed at our meeting, considerable useful information might be derived from such experiments. As the genomes of more and more viruses become better understood, I believe it will be possible to put the majority of the genes in any oncogenic virus (those genes dealing with functions other than transformation) into E. coli with virtually no risk. So it is with respect to whole viral genomes or the transforming genes from them that there is real controversy.

To answer directly the question you posed in your letter: I believe the existing moratorium should be modified to allow experimentation with bacteria containing chimeric molecules in which transforming genes from oncogenic viruses have been incorporated. I believe that it will be possible to handle such organisms in ways that present acceptably low risks, and I further believe that the potential benefits to be derived from working with such organisms are great. As I indicated in our meeting in November, I think a sensible first step would be to construct a sort of universal recipient strain of E. coli, which would be uvs, ts lethal, and streptomycin dependent. Whatever risk is associated with putting a chimeric DNA molecule into wild type E. coli will be very substantially decreased by using this strain instead. If, in addition, cells containing potentially hazardous chimeric DNA's are handled in the same way that pathogens are handled in standard bacteriological practice, a further substantial reduction in risk would occur. These handling procedures will require significant changes in the way people are used to handling E. coli, but will certainly allow work to continue at an acceptable level in most laboratories. These two measures should reduce what I think is an already small risk by many orders of magnitude. The classification of viruses into low, moderate, and high risk categories proposed by the NCI should be continued for bacteria containing transforming genes from these viruses, and precautions of increasing stringency should be applied to the handling of the presumably increasingly hazardous bacterial strains.

Best regards.

Sincerely yours,

Dave

David A. Jackson

DAJ:pjc